REMARKS

As a preliminary matter Applicants note that the copy of the Office Action mailed October 1, 2003, was incomplete and apparently missing at least one page. Applicants request that a full copy of the Office Action be supplied for Applicants' records.

Claim 1 has been amended to recite the use of vascular endothelial growth factor (VEGF) to treat hypertension. New dependent claims 2-10 are added. Support for new claims 2-10 can be found throughout the specification and claims as originally filed. See, for example, page 5, lines 20-29; page 25, line 13 to page 26, line 3; page 35, lines 18-26; and the Examples. Entry of the present amendment is respectfully requested.

The pending claims are fully supported by an enabling disclosure

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly claiming subject matter that was not described in the specification in such a way as to enable one of ordinary skill in the art to make and use the claimed invention. The test for enablement is whether one of ordinary skill in the art would be able to practice the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). The Office has alleged that because the specification used a salt-sensitive hypertension animal model, that one of ordinary skill in the art would not find the data produced from this model to be predictive for the use of the claimed method as a credible treatment of non-salt dependent hypertension. Presumably in the face of this alleged lack of predictability a skilled artisan would have to engage in undue experimentation to practice the claimed invention.

Claim 1 recites a method of treating hypertension by administering vascular endothelial growth factor (VEGF). The subject matter of the pending claims is supported by a specification that enables one of ordinary skill in the art to practice the claimed invention without undue experimentation. The pending claims relate to a method of treating hypertension comprising the administration of an effective amount of VEGF to lower the blood pressure of a patient. High blood pressure has been described in two forms, essential or primary hypertension and secondary

hypertension. The causes of essential hypertension are unknown. In secondary hypertension, the high blood pressure is secondary to or caused by a specific abnormality in one of the organs or systems of the body.

Essential hypertension is associated with people who have an intake of salt exceeding 5.8 grams daily. Excess salt intake may be involved in causing essential hypertension that is associated with advancing age, certain racial groups, obesity, hereditary susceptibility and renal insufficiency. Secondary hypertension is associated with renal damage that affects the Kidney ability to perform its osmoregulatory functions. The pending claims are directed to a method of treating hypertension comprising administering to a patient with an effective amount of a vascular endothelial growth factor (VEGF) regardless of the classification.

The specification provides detailed instructions regarding how to make VEGF preparations and to administer them to treat a patient with hypertension. For example, the specification discusses VEGF polypeptides taking a variety of forms, with a number of different mutations. Examples of such variations are described in U.S. Patent No. 5,332,671 and PCT Publication No. WO 98/36075, which were incorporated by reference in to the specification. (Specification, page 23, line 13 to page 24, line 11.) The specification also discusses making and delivering a variety of VEGF containing formulations (Specification, page 26 line 5 to page 31, line 18).

In view of these detailed teachings, one of ordinary skill in the art would not need to engage in undue experimentation to make and use the claimed invention. Accordingly, the present claims are fully supported by an enabling disclosure. As such, Applicants request that the present rejection be withdrawn.

Evidence of utility

Applicants respectfully disagree with the Office regarding the predictive nature of the experiments disclosed in the present specification. Nevertheless, solely to advance the prosecution of the present application, Applicants provided with this Amendment and Response a declaration in

accordance with Rule 37 CFR § 1.312 with evidence that administration of VEGF reduces blood pressure in an animal model of hypertension that is not salt dependent.

The evidence provided in the declaration demonstrates that the administration of VEGF lowers the blood pressure of rats presenting elevated blood pressure. As discussed in the declaration, rats were infected with an adenovirus encoding a soluble VEGF receptor sFlt(1-3). The VEGF receptor Flt-1 comprises seven IgG-like extracellular domains, a transmembrane domain and an intracellular domain. This receptor also is made in a soluble form that comprises the first 6 extracellular IgG-like domains and thus lacks the transmembrane domain (sFLT-1). The sFlt(1-3) is a soluble form of the receptor with the first three IgG-like domains of the native receptor. This fragment of the Flt-1 receptor is capable of binding VEGF.

Twelve rats were infected with the adenovirus vector comprising sFlt(1-3). Expression of the sFlt(1-3) protein was confirmed by the use of an immunological assay. The rats were randomly divided into a treated group and a control group. Rats in the treated group received approximately 100 µg/kg VEGF subcutaneously twice a day for seven (7) days while rats in the control group did not. Rats in the control group expressing the soluble VEGF receptor showed increased blood pressure, both systolic and diastolic (Exhibit 2). Rats treated with VEGF showed significantly reduced levels of systolic and diastolic blood pressure as compared to the control group. The blood pressure in the treated rats approached normal levels.

The data presented in the declaration clearly demonstrate that administration of VEGF is effective in lowering blood pressure in subjects. Moreover, the evidence provided demonstrates that the invention disclosed in the present application is effective to treat hypertension not caused by elevated salt levels. Thus, the scope of the present claims should not be limited to salt-dependent hypertension.

The present invention is supported by an adequate written description

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph, as purportedly not supported by an adequate written description. The test for an adequate written description requires

that one of ordinary skill in the art would reasonably conclude that the inventors were in possession of the claimed invention at the time the application was filed.

The pending claims now recite a method for treating hypertension comprising administering an effective dose of VEGF. The specification provides ample written support of the claimed method. For example, the specification explicitly states that "[t]he invention provides methods for treating hypertension." (Specification, page 35, lines 18-20.) Examples 2-5 of the specification describe experiments in which hypertension in rats was ameliorated by VEGF administration. In addition, the specification provides detailed teachings regarding the making and administration of VEGF compositions (see discussion above). Applicants respectfully submit that one of ordinary skill in the art, upon reviewing the present disclosure, would reasonably conclude that the inventors were in possession of the claimed invention at the time the application was filed.

The pending claims are novel over Rof, U.S. Patent No. 5,240,714

Claim 1 stands rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,240,714 (the "Rof patent"). To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). The pending claims recite a method of treating hypertension by administering VEGF. The Rof patent teaches the administration of a non-digoxin-like Na^+, K^+-ATPase inhibitory factor for a variety of purposes. The Rof patent does not, however, teach the administration of VEGF to treat hypertension. Because the Rof patent does not teach each and every limitation of the claimed invention, it does not anticipate the subject matter of the pending claims. Accordingly, the present rejection should be withdrawn.

In view of the discussion above Applicants submit that one of ordinary skill in the art would reasonably conclude from the teachings provided in the present specification that applicants were in possession of the claimed invention at the time the present application was filed. As such, withdrawal of the present rejection is requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 219002030901. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: 1 MAR, 2004 By: _____

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